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50381 OLIGONUCLEOTIDE?/BI
42114 OLIGONUCLEOTIDE?/AB
1663 ODN#/BI
1615 ODN#/AB
L1 51144 (OLIGONUCLEOTIDE? OR ODN#)/BI,AB

=> s (asthma? or desensit?)/bi,ab

16745 ASTHMA?/BI
14095 ASTHMA?/AB
16090 DESENSIT?/BI
15148 DESENSIT?/AB
L2 32695 (ASTHMA? OR DESENSIT?)/BI,AB

=> s l1 and l2

L3 150 L1 AND L2

=> s immunostim?/bi,ab

11525 IMMUNOSTIM?/BI
3753 IMMUNOSTIM?/AB
L4 11525 IMMUNOSTIM?/BI,AB

=> s l3 and l4

L5 15 L3 AND L4

=> s dinucleotide?/bi,ab

14700 DINUCLEOTIDE?/BI
8715 DINUCLEOTIDE?/AB
L6 14700 DINUCLEOTIDE?/BI,AB

=> s l5 and l6

L7 3 L5 AND L6

=> s l5 not 2001/py

481642 2001/PY
L8 4 L5 NOT 2001/PY

=> s l3 not 2001/py

481642 2001/PY
L9 92 L3 NOT 2001/PY

=> s l9 not 2000/py

961393 2000/PY
L10 57 L9 NOT 2000/PY

=> s l10 not 1999/py

910354 1999/PY
L11 39 L10 NOT 1999/PY

=> s l11 not 1998/py

894607 1998/PY
L12 28 L11 NOT 1998/PY

=> d l12 1-28 bib ab

L12 ANSWER 1 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1999:206805 CAPLUS
DN 131:30702
TI IL-5 and IL-5 receptor in asthma
AU Kotsimbos, A. T. C.; Hamid, Q.
CS Department of Medicine, Meakins-Christie Laboratories, McGill University, Montreal, PQ, H2X 2P2, Can.
SO Mem. Inst. Oswaldo Cruz (1997), 92(Suppl. 2), 75-91 CODEN: MIOCAS; ISSN: 0074-0276
PB Instituto Oswaldo Cruz
DT Journal; General Review
LA English
AB A review with approx. 150 refs. Activated T lymphocytes, interleukin-5 (IL5) prodn., and eosinophil activation are particularly important in the asthmatic response. Human studies in asthma and studies in allergic animal models have clearly emphasized the unique role of IL-5 in linking T lymphocytes and adaptive immunity, the eosinophil effector cell, and the asthma phenotype. The central role of activated lymphocytes and eosinophils in asthma would argue for the likely therapeutic success of strategies to block T cell and eosinophil activation (e.g. steroids). Importantly, more targeted therapies may avoid the complications assocd. with steroids. Such therapies could target key T cell activation proteins and cytokines by various means including blocking antibodies (e.g. anti-CD4, anti-CD40, anti-IL-5), antisense oligonucleotides to their specific mRNAs, and/or selective inhibition of the promoter sites for these genes. Another option would be to target key eosinophil activation mechanisms including the .alpha.IL5r. As always, the risk to benefit ratio of such strategies await the results of well conducted clin. trials.
RE.CNT 159
RE
(3) Azuma, C; Nucleic Acids Research 1986, V14, P9149 CAPLUS (5) Bazan, J; Proc Natl Acad Sci USA 1990, V87, P6934 CAPLUS (6) Bentley, A; Am J Resp Cell Mol Biol 1993, V8, P35 CAPLUS (10) Bischoff, S; J Exp Med 1990, V172, P1577 CAPLUS
(11) Boulay, J; Curr Opin Immunol 1992, V4, P294 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1997:723392 CAPLUS
DN 128:46335
TI Diadenosine polyphosphates evoke Ca2+ transients in guinea - pig brain via receptors distinct from those for ATP
AU Pintor, Jesus; Puche, Jose A.; Gualix, Javier; Hoyle, Charles H. V.; Miras-Portugal, Maria Teresa
CS Departamento de Bioquimica, Facultad de Veterinaria, Universidad Complutense, Madrid, 28040, Spain
SO J. Physiol. (Cambridge, U. K.) (1997), 504(2), 327-335 CODEN: JPHYA7; ISSN: 0022-3751
PB Cambridge University Press
DT Journal
LA English
AB The ability of diadenosine polyphosphates, namely P1,P2-di(adenosine) pyrophosphate (Ap2A), P1,P3-di(adenosine) triphosphate (Ap3A), P1,P4-di(adenosine) tetraphosphate (Ap4A), P1,P5-di(adenosine) pentaphosphate (Ap5A) and P1,P6-di(adenosine) hexaphosphate (Ap6A) to evoke Ca2+ signals in synaptosomes prepd. from three different regions of the guinea-pig brain was examd. In synaptosomal prepns. from the paleocortex (cortex), diencephalon/brainstem (midbrain) and cerebellum all the dinucleotides evoked Ca2+ signals that were concn. dependent over the range 1-300 .mu.M. ATP and its synthetic analogs, .alpha.,.beta.- methylene ATP, 2-methylthio ATP and adenosine 5'-O-(2-thio)diphosphate (all 100 .mu.M) also evoked Ca2+ signals in these prepns. In the midbrain and cerebellum prepns., responses to ATP and its analogs were attenuated or abolished by the P2 receptor antagonist suramin (100 .mu.M) but responses to the dinucleotides were not. Also, desensitization by a dinucleotide blocked responses to dinucleotides but not mononucleotides, and desensitization by a mononucleotide blocked responses to mononucleotides but not dinucleotides. In cortical prepns., suramin (100 .mu.M) blocked responses to both classes of

nucleotides. Furthermore, there was mutual cross-desensitization between the mono- and dinucleotides. The adenosine A1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine, did not affect responses evoked by the dinucleotides, nor did the pyrimidine UTP. It is concluded that there are specific dinucleotide receptors, activated by diadenosine polyphosphates, but not ATP or UTP, on synaptic terminals in guinea-pig diencephalon/brainstem and cerebellum. These receptors bear a similarity to the dinucleotide receptor (P4 receptor) in rat brain. In guinea-pig cerebral cortex synaptosomes, diadenosine polyphosphates appear to act via the same receptor as ATP.

L12 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1997:642136 CAPLUS
DN 127:317928
TI Optimized gene synthesis, high level expression, isotopic enrichment, and refolding of human interleukin-5
AU Mehta, Deepa V.; DiGate, Russel J.; Banville, Debra L.; Guiles, R. D. CS Dep. of Pharm. Sci., Sch. of Pharm., Univ. of Maryland at Baltimore, Baltimore, MD, 21201, USA
SO Protein Expression Purif. (1997), 11(1), 86-94
CODEN: PEXPEJ; ISSN: 1046-5928
PB Academic
DT Journal
LA English
AB Structural studies on sol. proteins using NMR spectroscopy and other structural methods in general require large quantities of isotopically enriched proteins. Human interleukin-5 is a disulfide-linked homodimeric cytokine implicated in asthmatic response. The development of a high yield overexpression system for human interleukin-5 is an important prerequisite to using modern multidimensional NMR in the characterization of the soln. structure of the protein and to characterize interactions with a sol. receptor domain. Significant amts. of the protein were expressed using an optimized synthetic gene in a high yield expression system. Gene synthesis was accomplished through the ligation of six oligonucleotides composed of optimized codons. The ligated fragments were further amplified by a polymerase chain reaction and then subcloned into the T7 RNA polymerase based overexpression vector pET11a. However, the induced protein accumulated in the form of inclusion bodies. Initially, the protein was solubilized under denaturing conditions and purified in these denaturing conditions by passage through a single S-200 HR sizing column. Finally, protein refolding was initiated in the presence of 2 M urea followed by dialysis. This protocol yielded 40 mg of biol. active, isotope-enriched protein from 4 L of minimal medium thus facilitating structural studies by NMR. The strategy described may be of immense value in the prodn. of significant quantities of recombinant, eukaryotic proteins for structural and other studies.

L12 ANSWER 4 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1997:628389 CAPLUS
DN 127:287450
TI Respirable antisense oligonucleotides as novel therapeutic agents for asthma and other pulmonary diseases AU Nyce, Jonathan W.
CS Department of Molecular Pharmacology and Therapeutics, EpiGenesis Pharmaceuticals, Inc., Durham, NC, 27707, USA
SO Expert Opin. Invest. Drugs (1997), 6(9), 1149-1156
CODEN: EOIDER; ISSN: 0967-8298
PB Ashley Publications
DT Journal; General Review
LA English
AB A review with 39 refs. Respirable antisense oligonucleotides (rAsONs) targeting discordantly expressed mediators of inflammation and/or bronchoconstriction and delivered to the lung via inhalation represent a new class of epigenetic-based therapeutics for asthma and other pulmonary diseases. The properties of these agents (soly., chem. stability, rapid design based on primary DNA sequence information) combine synergistically with characteristics of the lung (non-invasive route of administration directly to the target organ, presence of uptake-modifying surfactant) to enhance the therapeutic potential of these oligonucleotide -based drugs. Their potential is further increased by the possibility of engineering antisense oligonucleotides whose effects are limited to the lung, reducing or avoiding the possibility of systemic toxicity.

L12 ANSWER 5 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1997:628388 CAPLUS
DN 127:306259
TI Making sense of asthma
AU Richardson, Peter J.
CS Department of Pharmacology, University of Cambridge, Cambridge, CB2 1QJ, UK
SO Expert Opin. Invest. Drugs (1997), 6(9), 1143-1147
CODEN: EOIDER; ISSN: 0967-8298
PB Ashley Publications
DT Journal; General Review
LA English
AB A review and discussion with 39 refs. There is now a high probability that all the genes encoded in the human genome will have been sequenced by the year 2005, resulting in a massive increase in the identification of novel therapeutic targets. The use of new genomic sequence information in conjunction with antisense oligonucleotides is one means by which the gene products playing the most important roles in multifactorial diseases, such as asthma , can be identified. Subsequently, the antisense nucleotides themselves can be used as therapeutic agents, or drugs designed to control the activity of the relevant gene product.
L12 ANSWER 6 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1997:145753 CAPLUS
DN 126:246517

TI DNA antisense therapy for asthma in an animal model
AU Nyce, Jonathan W.; Metzger, W. James
CS Dep. Molecular Pharmacology, EpiGenesis Pharmaceuticals, Greenville, NC, 27834, USA
SO Nature (London) (1997), 385(6618), 721-725
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
AB Asthma is an inflammatory disease characterized by bronchial hyper-responsiveness that can proceed to life-threatening airway obstruction. It is one of the most common diseases in industrialized countries, and in the United States accounts for about 1% of all health care costs. Asthma prevalence and mortality have increased dramatically over the past decade, and occupational asthma is predicted to be the pre-eminent occupational lung disease in the next decade. Increasing evidence suggests that adenosine, an endogenous purine that is involved in normal physiol. processes, may be an important mediator of bronchial asthma . In contrast to normal individuals, asthmatic individuals respond to adenosine challenge with marked airway obstruction, and concns. of adenosine are elevated in the bronchoalveolar lavage fluid of asthma patients. We performed a randomized crossover study using the dust mite-conditioned allergic rabbit model of human asthma . Administration of an aerosolized phosphorothioate antisense oligodeoxynucleotide targeting the adenosine A1 receptor desensitized the animals to subsequent challenge with either adenosine or dust-mite allergen.

L12 ANSWER 7 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:757373 CAPLUS
DN 126:46181
TI Association between atopic asthma and a coding variant of Fc.epsilon.RI.beta. in a Japanese population. [Erratum to document cited in CA125:140337]
AU Shirakawa, T.; Mao, X.-Q.; Sasaki, S.; Enomoto, T.; Kawai, M.; Morimoto, K.; Hopkin, J.
CS Osler Chest Unit, Churchill Hospital, Oxford, UK
SO Hum. Mol. Genet. (1996), 5(12), 2068
CODEN: HMGEE5; ISSN: 0964-6906
PB Oxford University Press
DT Journal
LA English
AB The authors correct an oligonucleotide PCR primer sequence.

L12 ANSWER 8 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:741069 CAPLUS
DN 126:15076
TI Differential regional distribution of AMPA receptor subunit messenger RNAs in the human spinal cord as visualized by in situ hybridization AU Tomiyama, M.; Rodriguez-Pueertas, R.; Cortes, R.; Christnacher, A.; Sommer, B.; Pazos, A.; Palacios, J. M.; Mengod, G.
CS Department Neurochemistry, Instituto Investigaciones Biomedicas Barcelona, Barcelona, 08034, Spain
SO Neuroscience (Oxford) (1996), 75(3), 901-915
CODEN: NRSCDN; ISSN: 0306-4522
PB Elsevier
DT Journal
LA English
AB The electrophysiol. characteristics of .alpha.-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) receptors vary with their subunit compn. The establishment of the subunit distribution is an essential step in the understanding of the function of these receptors. In the spinal cord, AMPA receptors are involved in normal and, possibly, pathol. processes. Using in situ hybridization histochem. with radiolabeled oligonucleotides as probes, we have studied the distribution of AMPA receptor subunit mRNAs (spliced flip and flop variants of glutamate receptor subunits A-D) in the human post mortem spinal cord. Transcripts for flip variants were preferentially expressed in the superficial dorsal horn, with a dorsoventral decreasing gradient of the signals. Transcripts for flop variants were also abundantly present in all layers of the gray matter, with the highest signal being obsd. for glutamate receptor subunit Bflop. Accordingly, flop forms were predominant in areas other than the superficial dorsal horn. This differential distribution of transcripts in the dorsal horn suggests that the subunit compn. of AMPA receptors varies with the afferent inputs; AMPA receptors on neurons in the superficial dorsal horn, where terminals of thin primary afferents conducting noxious information are located, contain more flip forms, whereas neurons in the deep dorsal horn, where thick primary afferents mediating innocuous stimuli terminate, have AMPA receptors which are mainly composed of flop forms of glutamate receptor subunits A and B. The relatively high abundance of glutamate receptor subunit B transcripts in the superficial laminae of the dorsal horn indicates that AMPA receptors in these laminae have lower Ca2+ permeability. In addn., the relative abundance of glutamate receptor subunits Bflip and Dflop may show that AMPA receptors in the superficial dorsal horn have slow desensitization .

L12 ANSWER 9 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:576222 CAPLUS
DN 125:219497
TI Lack of association between atopy and the Ile181Leu variant of the beta-subunit of the high-affinity immunoglobulin E receptor AU Kofler, Heinz; Aichberger, Susanne; Ott, Gunter; Casari, Andrea; Kofler, Reinhard
CS Institute of General and Experimental Pathology, University of Innsbruck Medical School, Innsbruck, A-6020, Austria
SO Int. Arch. Allergy Immunol. (1996), 111(1), 44-47
CODEN: IAAIEG; ISSN: 1018-2438
DT Journal
LA English
AB A previous study has reported a strong assocn. of a variant (Ile181Leu) of the .beta.-subunit of the

high-affinity IgE receptor (Fc.epsilon.RI- .beta.) with allergic asthma bronchiale in a random patient sample. Based on their results the authors concluded that Fc.epsilon.RI-.beta. may be the maternally inherited, atopy-causing locus. We have investigated 40 unrelated atopic patients, 30 with allergic asthma and 10 with atopic dermatitis or allergic rhinoconjunctivitis along with some of their relatives for the presence of Ile181Leu by nucleic acid sequence anal. and/or hybridization with mutation-specific oligonucleotide probes. None of the probands showed this mutation suggesting that its assocn. with atopy may be restricted to certain populations or occur at lower frequency than reported.

L12 ANSWER 10 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:340167 CAPLUS
DN 125:1839
TI Involvement of G protein-coupled receptor kinase 5 in homologous desensitization of the thyrotropin receptor AU Nagayama, Yuki; Tanaka, Kunihiko; Hara, Takeshi; Namba, Hiroyuki; Yamashita, Shunichi; Taniyama, Kohtaro; Niwa, Masami
CS Dep. Pharmacol., Nagasaki Univ. Sch. Med., Nagasaski, 852, Japan SO J. Biol. Chem. (1996), 271(17), 10143-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Homologous desensitization of G protein-coupled receptors involves agonist-dependent phosphorylation of receptors by G protein-coupled receptor kinases (GRKs). To identify GRK(s) that play a role in homologous desensitization of the TSH receptor, thyroid cDNA was amplified by PCR using degenerate oligonucleotide primers from highly conserved regions in GRK family. GRK5 is found in the predominant isoform expressed in the thyroid. Rat GRK5 cDNA was then isolated, which encodes a 590-amino acid protein with 95% homol. to human and bovine homologs. Northern blot identified GRK5 mRNA of .apprx.3, 8, and 10 kilobases with highest expression levels in lung > hear, kidney, colon .gtoreq. thyroid. In functional studies using a normal rat thyroid FRTL5 cells, overexpression of GRK5 by transfecting the plasmid capable of expressing the sense GRK5 RNA suppressed basal cAMP levels and augmented the extent of TSH receptor desensitization , whereas suppression of endogenous GRK5 expression by transfecting the antisense GRK5 construct increased basal cAMP levels and attenuated the extent of receptor desensitization . Although exogenously overexpressed GRK6 also enhanced TSH receptor desensitization , the authors conclude that GRK5, the predominant GRK isoform in the thyroid, appears to be mainly involved in homologous desensitization of the TSH receptor.
L12 ANSWER 11 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:289132 CAPLUS
DN 124:334384
TI Molecular cloning of the gene for human leukotriene C4 synthase. Organization, nucleotide sequence, and chromosomal localization to 5q35 AU Penrose, John F.; Spector, Jeremy; Baldasaro, Mathew; Xu, Kongyi; Boyce, Joshua; Arm, Jonathan P.; Austen, K. Frank; Lam, Bing K. CS Dep. Medicine, Harvard Medical School, Boston, MA, 02115, USA SO J. Biol. Chem. (1996), 271(19), 11356-11361
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Leukotriene C4 (LTC4) synthase catalyzes the conjugation of LTA4 with reduced GSH to form LTC4, the parent of the receptor active cysteinyl leukotrienes implicated in the pathobiol. of bronchial asthma . Previous cloning of the cDNA for human LTC4 synthase demonstrated significant homol. of its amino acid sequence to that of 5-lipoxygenase activating protein (FLAP) but none to that of the GSH S-transferase superfamily. Genomic cloning from a P1 library now reveals that the gene for LTC4 synthase contains five exons (ranging from 71 to 257 nucleotides in length) and four introns, which in total span 2.52 kilobase pairs in length. The intron/exon junctions of LTC4 synthase align identically with those of FLAP; however, the small size of the LTC4 synthase gene contrasts with the >31-kilobase pair size reported for FLAP. Confirmation of the LTC4 synthase gene size to ensure that no deletions had occurred during the cloning was obtained by two overlapping polymerase chain reactions from genomic DNA, which provided products of the predicted sizes. Primer extension anal. with poly(A)+ RNA from culture-derived human eosinophilic granulocytes or the KG-1 myelogenous cell line revealed multiple transcriptional start sites with prominent signals at 66, 69, and 96 base pairs 5' of the ATG translation start site. The 5'-flanking region revealed a GC-rich promoter sequence consistent with an SP-1 site and consensus sequences for AP-1 and AP-2 enhancer elements, 24, 807, and 877 bp, resp., 5' from the first transcription initiation site. Southern blot anal. of a genomic DNA (with full-length cDNA as well as 5' and 3' oligonucleotide probes) confirmed the size of the gene and indicated a single copy gene in normal human genomic DNA. Fluorescent in situ hybridization mapped LTC4 synthase to chromosomal location 5q35, which is in close proximity to the cluster of genes for cytokines and receptors involved in the regulation of cells central to allergic inflammation and implicated in bronchial asthma .
L12 ANSWER 12 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:279986 CAPLUS
DN 125:1089
TI The endogenous benzodiazepine receptor ligand ODN increases cytosolic calcium in cultured rat astrocytes AU Lamacz, Marek; Tonon, Marie-Christine; Smih-Rouet, Fatima; Patte, Christine; Gasque, Philippe; Fontaine, Marc; Vaudry, Hubert CS European Institute for Peptide Research (IFRMP 23), Laboratory of Cellular and

Molecular Neuroendocrinology, INSERM U413, UA CNRS, University of Rouen, Mont-Saint-Aignan, 76821, Fr.
SO Mol. Brain Res. (1996), 37(1,2), 290-6
CODEN: MBREE4; ISSN: 0169-328X
DT Journal
LA English
AB We have investigated the prodn. of diazepam-binding inhibitor (DBI)-related peptides by astrocytes in primary culture and we have detd. the effect of the octadecaneuropeptide DBI[33-50] (ODN) on the intracellular calcium concn. ([Ca2+]i) in astrocytes. Immunocytochem. labeling with antibodies against ODN showed that cultured astrocytes retain their ability to synthesize DBI in vitro. Cultured astrocytes were also found to release substantial amts. of ODN -immunoreactive material, and a brief exposure of astrocytes to a depolarizing potassium concn. resulted in a 5-fold increase in the rate of release of the ODN -like peptide. Microfluorimetric measurement of [Ca2+]i with the fluorescent probe indo-1 showed that nanomolar concns. of ODN induced a marked increase in [Ca2+]i. The stimulatory effect of ODN on [Ca2+]i was not affected by calcium channel blockers or by incubation in Ca2+-free medium. In contrast, thapsigargin, an inhibitor of microsomal Ca2+-ATPase activity, totally abolished the ODN -induced increase in [Ca2+]i. Repeated pulses of ODN caused attenuation of the response, indicating the existence of a desensitization phenomenon. Preincubation of astrocytes with pertussis toxin totally blocked the effect of ODN on [Ca2+]i. The present study indicates that ODN -related peptides are synthesized and released by glial cells. Our results also show that synthetic ODN induces calcium mobilization from an intracellular store through stimulation of pertussis toxin-sensitive G protein. Taken together, these data suggest that endozepines act as paracrine and/or autocrine factors controlling the activity of astroglial cells.

L12 ANSWER 13 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1996:204746 CAPLUS
DN 124:313430
TI The proteinase activated receptor-2 (PAR-2) mediates mitogenic responses in human vascular endothelial cells: molecular characterization and evidence for functional coupling to thrombin receptor
AU Mirza, Humayun; Yatsula, Victoria; Bahou, Wadie F.
CS Dep. Medicine, State Univ. New York Stony Brook, Stony Brook, NY, 11794-8151, USA
SO J. Clin. Invest. (1996), 97(7), 1705-14
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB Proteolytically cleaved receptors, typified by the functional thrombin receptor (TR), represent a novel class of receptors that mediate signaling events by functional coupling to G proteins. Northern blot anal. completed with a human proteinase activated receptor-2 (PAR-2) cDNA as probe demonstrated the .apprx.3.5 kb PAR-2 transcript in total cellular RNA from human umbilical vein endothelial cells (HUVEC). Microspectrofluorimetry using Fura2-loaded HUVEC demonstrated a dose-dependent elevation in intracellular calcium transients ([Ca2+]i) to murine PAR39-44 (SLIGRL, putative neoligand after cleavage), with an .apprx.EC50 of 30 .mu.M, and evidence for homologous desensitization with complete recovery at 45 min. Xenopus oocytes microinjected with TR cRNA failed to respond to 200 .mu.M PAR39-44, and TR-targeted antisense oligonucleotides specifically abrogated thrombin-induced but not PAR39-44-mediated [Ca2+]i, excluding the possibility that TR/PAR-2 cell-surface coexpression was structurally linked. HUVEC incubated with PAR39-44 demonstrated a dose- and time-dependent mitogenic response similar to that seen with thrombin or TR42-47 (TR-activating peptide, SFLLRN). Preactivation of HUVEC with either PAR39-44 or thrombin resulted in heterologous desensitization to the corresponding agonist, an effect that was mediated primarily by TR internalization as evaluated by immunofluorescence and quant. ELISA. These results ascribe a previously unrecognized function to the PAR-2 receptor, imply that a natural enzyme agonist may circulate in plasma, and suggest that presence of an addnl. regulator mechanism controlling receptor activation events in vascular endothelial cells.

L12 ANSWER 14 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1995:581396 CAPLUS
DN 123:196398
TI A nuclear factor of activated T cell-like transcription factor in mast cells is involved in IL-5 gene regulation after IgE plus antigen stimulation
AU Prieschl, Eva E.; Gouilleux-Gruart, Valerie; Walker, Christoph; Harrer, Nathalie E.; Baumruker, Thomas
CS Dep. Immunodermatology, Sandoz Forschungsinstitut, Vienna, Austria SO J. Immunol. (1995), 154(11), 6112-19
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
AB IL-5, which is produced mainly by activated T cells and allergically triggered mast cells, is a major survival and differentiation factor for eosinophils, and therefore, is of relevance to diseases assocd. with this type of cell infiltration, most importantly asthma . In this study, the authors examd. the transcriptional regulation of human IL-5 in a mouse mast cell line, CPII, stimulated with IgE and Ag. The authors report that an inducible activity in the region between -177 and -80, and a constitutive activity between -80 and -70, in the promoter of the human gene, are both necessary for the allergically triggered activation. A computer-assisted search for transcription factor binding motifs revealed a nuclear factor of activated T cell (NF-AT) and a GATA consensus site in the two regions. Corresponding

binding activities were detected to be present in nuclear exts. from the mouse mast cell line by defined NF-AT and GATA binding sites as probes for a gel shift anal. Competition anal., in combination with probes from the human IL-5 promoter, confirmed that these factors indeed bind to the consensus sequences identified by computer anal. An oligonucleotide spanning the IL-5 NF-AT consensus site is shown to confer allergic stimulation to a basal IL-5 promoter only in conjunction with the GATA site downstream, indicating that an inducible NF-AT-like factor cooperates with a constitutive member of the GATA transcription factor family in mediating the allergic stimulation of the human IL-5 gene.

L12 ANSWER 15 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1995:388114 CAPLUS
DN 122:157622
TI Regulation of .beta.-adrenergic receptors in acute myocardial ischemia: subtype-selective increase of mRNA specific for .beta.1-adrenergic receptors
AU Ihl-Vahl, R.; Marquetant, R.; Bremerich, J.; Strasser, R. H. CS Department of Cardiology, Univ. of Heidelberg, Heidelberg, 69120, Germany SO J. Mol. Cell. Cardiol. (1995), 27(1), 437-52
CODEN: JMCDAY; ISSN: 0022-2828
DT Journal
LA English
AB Acute myocardial ischemia leads to a rapid increase of cardiac .beta.-adrenergic receptors in plasma membranes despite the release of large and desensitizing amts. of endogenous catecholamines. Part of this increase has been shown to occur at the expense of intracellular receptors. To investigate whether an addnl. expressional regulation of .beta.-adrenergic receptors due to an increase of mRNA levels in involved, the mRNA levels specific for .beta.1- and .beta.2-adrenergic receptors were detd. after various periods of global ischemia in isolated perfused rat hearts. The subtype-specific quantification of mRNA for .beta.1- and .beta.2-adrenergic receptors was detd. using reverse-transcription followed by PCR (TR-PCR) and RNA protection assays. RT-PCR resulted in single amplification products of the expected sizes (159 bp for .beta.1-adrenergic receptors and 240 bp for .beta.2-adrenergic receptors). The specificity of these amplification products was confirmed by specific restriction digests, Southern blot hybridizations with internal oligonucleotides and sequencing using the dideoxy chain termination method. For quantification purposes, the mRNAs of housekeeping gene GAPDH and of cardiac .alpha.-actin were detd. as internal stds. Addnl., cRNAs specific for .beta.1- and .beta.2-adrenergic receptors were used as external stds. Brief periods of global ischemia induced a rapid increase in the steady state level of mRNA for .beta.1-adrenergic receptors. There was a statistically significant rise already after 15 min by 57% compared to controls. After 30 min of ischemia the mRNA levels had almost doubled. After 60 min of ischemia, the mRNA levels specific for mRNA levels specific for .beta.1-adrenergic receptors tended to decrease, but remained significantly above normoxic controls. In contrast, the mRNA levels specific for .beta.2-adrenergic receptors remained const. up to 60 min of global myocardial ischemia. To investigate, whether agonist occupancy of the receptors may contribute to this regulation, the effect of preperfusion with the .beta.-blocker alprenolol was detd. Contrary to expectation, .beta.-blockade did not influence the ischemia-induced increase of mRNA levels specific for .beta.1-adrenergic receptors. Evidently, acute myocardial ischemia induces a rapid, and subtype-selective regulation of mRNA levels for .beta.1-adrenergic receptors. However, occupation or activation of .beta.-adrenergic receptors by an agonist is not involved in this newly characterized regulation of mRNA for .beta.1-adrenergic receptors in acute myocardial ischemia.

L12 ANSWER 16 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1995:122831 CAPLUS
DN 122:26638
TI Molecular cloning and expression of human leukotriene-C4 synthase AU Welsch, Dean J.; Creely, David P.; Hauser, Scott D.; Mathis, Karl J.; Krivi, Gwen G.; Isakson, Peter C.
CS Searle Res. Dev., Monsanto Co., St. Louis, MO, 63198, USA SO Proc. Natl. Acad. Sci. U. S. A. (1994), 91(21), 9745-9 CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Leukotriene-C4 synthase (LTC4S; EC 2.5.1.37) catalyzes the committed step in the biosynthesis of the peptidoleukotrienes, which are important in the pathogenesis of asthma . Antibodies were generated to a synthetic peptide based on the partial amino acid sequence previously reported for human LTC4S and specifically bound detergent-solubilized LTC4S obtained from THP-1 cells, confirming that the published sequence is assocd. with enzyme activity. Inosine-contg. oligonucleotides based on the partial protein sequence were used to isolate a 679-bp cDNA for LTC4S from THP-1 cells. The cDNA contains an open reading frame that encodes a 150-amino acid protein (Mr = 16,568) that has a calcd. pI value of 11.1. The deduced protein sequence is composed predominantly of hydrophobic amino acids; hydropathy anal. predicts 3 transmembrane domains connected by 2 hydrophilic loops. Anal. of the deduced sequence identified 2 potential protein kinase C phosphorylation sites and a potential N-linked glycosylation site. The amino acid sequence for human LTC4S is unique and shows no homol. to other glutathione S-transferases. LTC4S was most similar to 5-lipoxygenase activating protein (31% identity, 53% similarity), another protein involved in leukotriene biosynthesis. Active enzyme was expressed in bacterial, insect, and mammalian cells as shown by the biosynthesis of LTC4 in incubation mixts. contg.

LTA4 and reduced glutathione. The cloning and expression of human LTC4S provide the basis for a better understanding of this key enzyme in peptidoleukotriene biosynthesis.

L12 ANSWER 17 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1994:597081 CAPLUS
DN 121:197081
TI Expression cloning of a dust mite cysteine proteinase Der pI, a major allergen associated with asthma and hypersensitivity reactions AU Scobie, G.; Ravindran, V.; Deam, S. M.; Thomas, M.; Sreedharan, S. K.; Brocklehurst, K.; Kalsheker, N.
CS Dep. Clinical Chem., Queen's Med. Cent., Nottingham, NG7 2UH, UK SO Biochem. Soc. Trans. (1994), 22(4), 448S
CODEN: BCSTB5; ISSN: 0300-5127
DT Journal
LA English
AB Total RNA from Dermatophagoides pteronyssinus was prepd., cDNA synthesized using reverse transcriptase and a specific oligonucleotide to the allergen Der pI, and the cDNA amplified and ligated to the .beta.-galactosidase gene in a pin-point expression vector. The clone used for expression was identical to the published sequence of Der pI except for a Val124Ala substitution. A fusion protein of the expected size was generated that showed some immunoreactivity, but it was catalytically inactive.

L12 ANSWER 18 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1994:427843 CAPLUS
DN 121:27843
TI The GTPase Rab3a negatively controls calcium-dependent exocytosis in neuroendocrine cells
AU Johannes, Ludger; Lledo, Pierre Marie; Roa, Michele; Vincent, Jean Didier; Henry, Jean Pierre; Darchen, Francois
CS Inst. Biol. Phys. Chim., Paris, 75005, Fr.
SO EMBO J. (1994), 13(9), 2029-37
CODEN: EMJODG; ISSN: 0261-4189
DT Journal
LA English
AB There is accumulating evidence that small GTPases of the rab family regulate intracellular vesicle traffic along biosynthetic and endocytotic pathways in eukaryotic cells. It has been suggested that Rab3a, which is assocd. with synaptic vesicles in neurons and with secretory granules in adrenal chromaffin cells, might regulate exocytosis. The authors report here that overexpression in PC12 cells of Rab3a mutant proteins defective in either GTP hydrolysis or in guanine nucleotide binding inhibited exocytosis, as measured by a double indirect immunofluorescence assay. Moreover, injection of the purified mutant proteins into bovine adrenal chromaffin cells also inhibited exocytosis, as monitored by membrane capacitance measurements. Finally, the electrophysiol. approach showed that bovine chromaffin cells which were intracellularly injected with antisense oligonucleotides targeted to the Rab3a messenger exhibited an increasing potential to respond to repetitive stimulations. In contrast, control cells showed a phenomenon of desensitization . These results provide clear evidence that Rab3a is involved in regulated exocytosis and suggest that Rab3a is a regulatory factor that prevents exocytosis from occurring unless secretion is triggered. Furthermore, it is proposed that Rab3a is involved in adaptive processes such as response habituation.

L12 ANSWER 19 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1993:643793 CAPLUS
DN 119:243793
TI Cloning and characterization of an endothelin-3 specific receptor (ETC receptor) from Xenopus laevis dermal melanophores
AU Karne, Suresh; Jayawickreme, Channa K.; Lerner, Michael R. CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SO J. Biol. Chem. (1993), 268(25), 19126-33
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The authors report here the presence of a receptor specific for endothelin-3 (termed ETC receptor or ETCR) on Xenopus laevis dermal melanophores. Activation of ETCR causes the dispersion of the pigment granules within the melanophores. The EC50 for ET-3 to induce the pigment dispersion is 24 .+-. 7 nM, compared to greater than 10 .mu.M for both ET-1 and -2. This effect desensitizes in a manner that is dependent on both time and the concn. of ET-3 used to stimulate the cells. A cDNA encoding for ETCR was isolated by a polymerase chain reaction-mediated DNA amplification strategy using degenerate oligonucleotides prepd. based on conserved regions of other known G-protein-coupled receptor sequences and by the subsequent screening of a frog melanophore cDNA library. The cloned cDNA consists of 2,240 nucleotides, with an open reading frame coding for 444 amino acids contg. an initial 20-amino acid signal sequence. The predicted mature peptide consists of 424 amino acids with a heptahelical structure common to the G-protein-coupled receptor superfamily. Its deduced amino acid sequence is 47 and 52% identical to ETA and ETB receptors, resp., while ETA and ETB are 48% identical to each other. Expression of cDNA in HeLa cells, which do not contain endothelin receptors, enables the cells to specifically bind[125I]ET-3. Competition binding expts. performed on HeLa cells transiently expressing pETC show that the apparent Ki values for ET-3 and ET-1 to displace [125I]ET-3 are 45.5.+-. 16 and 114 .+-. 22 nM, resp.

L12 ANSWER 20 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1993:554855 CAPLUS
DN 119:154855
TI Liver adenylyl cyclases: Structure and regulation by cAMP-dependent phosphorylation
AU Premont, Richard T.; Iyengar, Ravi

CS Dep. Pharmacol., Mount Sinai Med. Cent., New York, NY, 10029, USA SO Adenine Nucleotides Cell. Energy Transfer Signal Transduction (1992), 325-34. Editor(s): Papa, Sergio; Azzi, Angelo; Tager, Joseph M. Publisher: Birkhaeuser, Basel, Switz.
CODEN: 59IHAJ
DT Conference
LA English
AB Two distinct adenylyl cyclases have been cloned from a rat liver cDNA library. These sequences share 70% identity, as compared to 30-35% shared identity among other cloned members of this enzyme family, indicating that these two liver forms comprise a distinct subfamily of adenylyl cyclases. The two liver adenylyl cyclase sequences have been identified in all tissues so far examd. by polymerase chain reaction (PCR) amplification of first-strand cDNAs from specific oligonucleotide primers. Unlike other cloned forms of adenylyl cyclase with limited distributions, these two adenylyl cyclases have the wide distribution expected for the "ubiquitous" Gs-regulated adenylyl cyclase activity in mammalian tissues. The mouse homolog of one of these adenylyl cyclases has been identified in the S49 lymphoma cell line. The liver (and S49 cell) adenylyl cyclases share a single conserved protein kinase A consensus phosphorylation site, which may be involved in inhibitory regulation of adenylyl cyclase activity during heterologous desensitization .

L12 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1993:251807 CAPLUS
DN 118:251807
TI Role of protein phosphorylation and dephosphorylation in activation and desensitization of the cAMP-dependent sodium/hydrogen ion antiport AU Guizouarn, Helene; Borgese, Franck; Pellissier, Bernard; Garcia-Romeu, Federico; Motais, Rene
CS Dep. Biol., CEA, Villefranche-sur-Mer, 06230, Fr. SO J. Biol. Chem. (1993), 268(12), 8632-9
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The Na+/H+ antiporter of trout erythrocytes is activated by agents raising intracellular cAMP, whereas other Na+/H+ exchangers are insensitive to or inhibited by cAMP. Cloning of the .beta. agonist-activated exchanger (.beta.NHE) reveals the presence of two consensus sites for phosphorylation by the cAMP-dependent protein kinase A (cAMP-PKA) on the cytoplasmic loop. Transfected to fibroblasts, .beta.NHE can no longer be activated by cAMP when those consensus sites are removed, indicating regulation through cAMP-PKA. Moreover, it has been shown that activation of the exchanger is rapidly followed by its desensitization . To further investigate the role of phosphorylation in these processes, the effects of protein kinase and phosphatase inhibitors on the antiporter activation and desensitization in trout red cells were examd. Na+/H+ exchange was not induced by strong acidification, indicating that .beta.NHE is normally in a nonfunctional state, whereas cAMP did activate the system by forcing .beta.NHE into a functional conformation; preincubation of cells with the kinase inhibitor H89 blocked cAMP-activation, confirming the role of cAMP-PKA in the activation process. The protein phosphatase inhibitor okadaic acid (OA) neither activated the exchange when added on unstimulated cells nor prevented deactivation of .beta. agonist-activated .beta.NHE by propranolol. Hence, the cAMP-dependent phosphorylation involved in the activating process is controlled by an OA-insensitive phosphatase. .beta.NHE activated by .beta. agonist or cAMP shifts rapidly into a refractory state, accounting for the previously described desensitization . Desensitization was blocked and reversed by OA, indicating a control by an OA-sensitive phosphatase of the phosphorylation level of a site crit. for the desensitizing process. Phosphorylation of this (site 2) and of the activating site (site 1) is mediated by cAMP-PKA, as demonstrated by the effects of both intracellular cAMP concn. and kinase inhibitor H89 on the Na+/H+ exchange activity. Based on these data, it was proposed that .beta.NHE can exist in 3 different states: inactive I, activated A, and desensitized D. Conversion of I to A needs the simultaneous phosphorylation by cAMP-PKA of sites 1 and 2. These 2 sites might constitute the 2 neighboring cAMP-PKA sites located on the cytoplasmic loop as deduced from the oligonucleotide sequence. Dephosphorylation of site 2 and subsequent binding of an arrestin-like protein are assumed to account for desensitization of the antiport. This putative role of arrestin is inferred from previous results demonstrating the presence in trout red cells (immunol. detection and cloning) of such a protein, which in addn. has been shown to bind to bovine rhodopsin as does retinal arrestin which participates in rhodopsin desensitization .

L12 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1992:549057 CAPLUS
DN 117:149057
TI Characterization of two high affinity human interleukin-8 receptors AU Lee, James; Horuk, Richard; Rice, Glenn C.; Bennett, Gregory L.; Camerato, Tom; Wood, William I.
CS Dep. Mol. Biol., Genentech, Inc., South San Francisco, CA, 94080, USA SO J. Biol. Chem. (1992), 267(23), 16283-7
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Interleukin 8 (IL-8) and melanocyte growth-stimulatory activity/gro (MGSA) are structurally related proinflammatory cytokines that are chemoattractants and activators of neutrophils. Recently, cDNA clones encoding a high affinity IL-8 receptor (IL-8R-A) and a low affinity IL-8 receptor (IL-8R-B) have been isolated from human cDNA

libraries. These 2 receptors have 77% amino acid identity and are members of the G protein-coupled superfamily of receptors with 7 transmembrane domains. Here, these 2 receptors were expressed in mammalian cells and, in this system, both receptors bind IL-8 with high affinity (Kd .apprx.2 nM). The receptor affinities differ for MGSA, however. IL-8R-A binds MGSA with low affinity (Kd .apprx.450 nM); IL-8R-B binds MGSA with high affinity (Kd .apprx.2 nM). The transfected cells respond to ligand binding with a transient increase in the intracellular Ca2+ concn. A Ca2+ response is found for IL-8R-A following the binding of IL-8; no response is found for MGSA. A Ca2+ response for IL-8R-B follows the binding of both ligands. Blot hybridization with oligonucleotide probes specific for the 2 receptors shows that mRNA for both receptors is present in human neutrophils. Anal. of IL-8 and MGSA binding data on neutrophils as well as Ca2+ response and desensitization data shows that the presence of these 2 IL-8 receptors on the cell surface can account for the profile of these 2 ligands on neutrophils.

L12 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1990:609757 CAPLUS
DN 113:209757
TI Interleukin 1 induces .beta.-endorphin secretion via Fos and Jun in AtT-20 pituitary cells
AU Fagarasan, Mirela O.; Aiello, Francesca; Muegge, Katherin; Durum, Scott; Axelrod, Julius
CS Lab. Cell. Biol., Natl. Inst. Ment. Health, Bethesda, MD, 20892, USA SO Proc. Natl. Acad. Sci. U. S. A. (1990), 87(20), 7871-4 CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB Previous work has been shown that interleukin 1 (IL-1), after a long period of treatment, stimulates .beta.-endorphin release and potentiates the effects of secretagogues in AtT-20 cells, a mouse anterior pituitary cell line. Treatment of AtT-20 cells with IL-1 induced a transient and early stimulation of mRNA expression by both immediate-early protooncogenes Fos and Jun (mouse c-fos and c-jun). The effect appeared within 30 min, and returned to basal levels after 2 h. Desensitization of protein kinase C by phorbol ester pretreatment had no effect on the ability of IL-1 to induce Fos and Jun mRNA expression. Somatostatin, an inhibitor of cAMP and .beta.-endorphin secretion, did not reduce the IL-1 effect on Fos and Jun mRNA expression. Addn. to AtT-20 cells of antisense oligonucleotides to Fos and Jun abolished the secretion induced by IL-1. Thus, immediate-early signals Fos and Jun are involved in IL-1-induced .beta.-endorphin secretion in AtT-20 cells.

L12 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1990:174749 CAPLUS
DN 112:174749
TI .beta.-Adrenergic receptor kinase: primary structure delineates a multigene family
AU Benovic, Jeffrey L.; DeBlasi, Antonio; Stone, W. Carl; Caron, Marc G.; Lefkowitz, Robert J.
CS Howard Hughes Med. Inst., Duke Univ., Durham, NC, 27710, USA SO Science (Washington, D. C., 1883-) (1989), 246(4927), 235-40 CODEN: SCIEAS; ISSN: 0036-8075
DT Journal
LA English
AB The .beta.-adrenergic receptor kinase (.beta.-ARK), which specifically phosphorylates only the agonist-occupied form of the .beta.-adrenergic and closely related receptors, appears to be important in mediating rapid agonist-specific (homologous) desensitization . The structure of this enzyme was elucidated by isolating clones from a bovine brain cDNA library through the use of oligonucleotide probes derived from partial amino acid sequence. The .beta.-ARK cDNA codes for a protein of 689 amino acids (79.7 kilodaltons) with a protein kinase catalytic domain that bears greatest sequence similarity to protein kinase C and the cAMP-dependent protein kinase. When this clone was inserted into a mammalian expression vector and transfected into COS-7 cells, a protein that specifically phosphorylated the agonist-occupied form of the .beta.2-adrenergic receptor and phosphorylated, much more weakly, the light-bleached form of rhodopsin was expressed. RNA blot anal. revealed a mRNA of 4 kilobases with highest amts. in brain and spleen. Genomic DNA blot anal. also suggests that .beta.-ARK may be the first sequenced member of a multigene family of receptor kinases.

L12 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1990:49256 CAPLUS
DN 112:49256
TI Modification of the rat adipocyte A1 adenosine receptor-adenylate cyclase system during chronic exposure to an A1 adenosine receptor agonist: alterations in the quantity of GS.alpha. and Gi.alpha. are not associated with changes in their mRNAs
AU Longabaugh, J. Peter; Didsbury, John; Spiegel, Allen; Stiles, Gary L. CS Med. Cent., Duke Univ., Durham, NC, 27710, USA
SO Mol. Pharmacol. (1989), 36(5), 681-8
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB The A1-adenosine receptor (A1AR) adenylate cyclase system in rat adipocytes undergoes heterologous desensitization following chronic in vivo exposure to an A1AR agonist (+)-N6-(R- phenylisopropyl)adenosine. This desensitization involved an abs. increase in adenylate cyclase activity and refractoriness to receptor ligands that are inhibitory to adenylate cyclase. In this study, receptor changes were characterized using an A1AR antagonist radioligand, [3H]8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropyl xanthine. Satn. binding studies

demonstrated a 47% decrease in total A1AR d. without a change in KD. Agonist competition studies revealed a decreased percentage of receptors, from 55% to 35%, in the high affinity state following desensitization . An increase in Gs.alpha. of 49% was found by Western blotting using specific Gs.alpha. antibodies. Further, an antibody that recognizeds Gi.alpha.1 and Gi.alpha.2 was used to quanitate these subtypes of Gi.alpha. and both were decreased by 59% following desensitization . However, when an antibody that recognizes Gi.alpha.3 was used, no change in Gi.alpha.3 was found, demonstrating, in this case, differential regulation of Gi.alpha. subtypes. The mechanisms responsible for changes in Gs.alpha. and Gi.alpha. were studied by measuring the levels of their mRNA from normal and desensitized adipocytes. Using either labeled cDNAs (Gi.alpha.2, Gi.alpha.3) or oligonucleotides (Gs.alpha., Gi.alpha.1), Northern anal. demonstrated that mRNAs for Gs.alpha. and all 3 isoforms of Gi.alpha. are present in adipocytes but that there are no changes in the levels of any of these transcripts following desensitization . Apparently, desensitization of the A1AR-adenylate cyclase system involves a downregulation of A1ARs and an addnl. loss of A1AR agonist high affinity sites. Further, an increase in Gs.alpha., a decrease in Gi.alpha.1 and Gi.alpha.2, and no change in G2.alpha.3 were found. The regulation of Gs.alpha. and the subtypes of Gi.alpha. in this system does not occur by altering the levels of their resp. transcripts.

L12 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1989:110403 CAPLUS
DN 110:110403
TI Agonist-promoted sequestration of the .beta.2-adrenergic receptor requires regions involved in functional coupling with Gs
AU Cheung, Anne H.; Sigal, Irving S.; Dixon, Richard A. F.; Strader, Catherine D.
CS Dep. Biochem. Mol. Biol., Merck, Sharp, and Dohme Res. Lab., Rahway, NJ, 07065, USA
SO Mol. Pharmacol. (1989), 35(1), 132-8
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB The mol. basis for the desensitization of .beta.2-adrenergic receptors was investigated by oligonucleotide -directed mutagenesis. .beta.-Adrenergic receptor mutants contg. deletions within the 6th hydrophilic domain that failed to couple to protein Gs and stimulate adenylate cyclase did not undergo agonist-mediated sequestration. In contrast, all receptor mutants that displayed protein Gs coupling were sequestered away from the cell surface in response to isoproterenol. Progressive truncation of the C-terminus of the receptor resulted in decreases in the initial rates of receptor sequestration and functional uncoupling, although the final extent of these desensitization processes was not affected by the mutations. Thus, structural features of the .beta.2-adrenergic receptor that are involved in receptor activation are probably also essential for mediating the subsequent inactivation caused by the sequestration of the receptor from the cell surface.

L12 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1988:88398 CAPLUS
DN 108:88398
TI The carboxyl terminus of the hamster .beta.-adrenergic receptor expressed in mouse L cells is not required for receptor sequestration AU Strader, Catherine D.; Sigal, Irving S.; Blake, Allan D.; Cheung, Anne H.; Register, R. Bruce; Rands, Elaine; Zemcik, Barbara A.; Candelore, Mari Rios; Dixon, Richard A. F.
CS Dep. Biochem. Mol. Biol., Merck Sharp and Dohme Res. Lab., Rahway, NJ, 07065, USA
SO Cell (Cambridge, Mass.) (1987), 49(6), 855-63
CODEN: CELLB5; ISSN: 0092-8674
DT Journal
LA English
AB The structural basis for agonist-mediated sequestration and desensitization of the .beta.-adrenergic receptor was examd. by oligonucleotide -directed mutagenesis of the hamster .beta.-adrenergic receptor gene and expression of the mutant genes in mouse L cells. Treatment of these cells with the agonist isoproterenol corresponded to a desensitization of .beta.-adrenergic receptor activity. A mutant receptor that bound agonist but did not couple to adenylate cyclase showed a lower sequestration response to agonist stimulation. In contrast, .beta.-adrenergic receptor mutants in which the C-terminus was truncated and(or) in which two regions that have been proposed as phosphorylation substrates for cAMP-dependent protein kinase were removed, showed normal sequestration responses. Apparently, agonist-mediated sequestration of the .beta.-adrenergic receptor can occur in the absence of the C-terminus of the protein, and there is a strong correlation between effective coupling to stimulatory guanine nucleotide-binding proteins and sequestration.

L12 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2001 ACS
AN 1986:620014 CAPLUS
DN 105:220014
TI Phenotypic changes induced by a mutated ras gene during the development of Dictyostelium transformants
AU Reymond, Christophe D.; Gomer, Richard H.; Nellen, Wolfgang; Theibert, Anne; Devreotes, Peter; Firtel, Richard A.
CS Cent. Mol. Genet., Univ. California, La Jolla, CA, 92093, USA SO Nature (London) (1986), 323(6086), 340-3
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB The effects of a glycine-12 to threonine-12 c-ras gene missense mutation on the development of Dictyostelium were examd. The mutant was obtained by

oligonucleotide -directed mutagenesis. In contrast to the wild-type cells, the mutants on Millipore filters formed multiple-tipped aggregates that did not fruit. In a submerged culture, the mutants did not form aggregation streams, whereas wild-type cells formed large aggregation streams. The cAMP receptor levels, effect of guanine nucleotides on the affinity of cAMP on the receptor, ligand-induced receptor phosphorylation, and cAMP- and guanylnucleotide-dependent activation and desensitization of adenylate cyclase [9012-42-4] were not substantially altered in the mutants.

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